

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/011009

|   |   |   |
|---|---|---|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 C12Q1/68  |   |   |
| According to International Patent Classification (IPC) or to both national classification and IPC   |   |   |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C12Q  |   |   |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |   |   |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data, PAJ  |   |   |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |   |   |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.   |
| X   | FOEKENS J A ET AL: "PROGNOSTIC SIGNIFICANCE OF CATHEPSINS B AND L IN PRIMARY HUMAN BREAST CANCER" JOURNAL OF CLINICAL ONCOLOGY, GRUNE AND STRATTON, NEW YORK, NY, US, vol. 16, no. 3, 1998, pages 1013-1021, XP001068659<br>ISSN: 0732-183X<br>page 1013 - page 1014<br>page 1015, left-hand column, paragraph 2<br><div style="text-align: center;">-----<br/>-/--</div> | 3,4,12, 17,18   |
| <div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>   |   |   |
| * Special categories of cited documents :   |   |   |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div> |   |   |
| Date of the actual completion of the international search<br><br><div style="text-align: center;">17 December 2004</div>  |   | Date of mailing of the international search report<br><br><div style="text-align: center;">26. 01. 2005</div> |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  |   | Authorized officer<br><br><div style="text-align: center;">Knudsen, H</div>                                   |

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
|--|---|-----------------------|
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| X  | <p>YAN SHIQING ET AL: "Cathepsin B and human tumor progression"<br/>BIOLOGICAL CHEMISTRY,<br/>vol. 379, no. 2, February 1998 (1998-02),<br/>pages 113-123, XP009040634<br/>ISSN: 1431-6730<br/>page 113, right-hand column - page 114,<br/>left-hand column<br/>page 119, right-hand column</p>   | 3,4,17,<br>18         |
| X  | <p>PREMZL ALES ET AL: "Intracellular and extracellular cathepsin B facilitate invasion of MCF-10A neoT cells through reconstituted extracellular matrix in vitro."<br/>EXPERIMENTAL CELL RESEARCH. 15 FEB 2003,<br/>vol. 283, no. 2,<br/>15 February 2003 (2003-02-15), pages<br/>206-214, XP002308364<br/>ISSN: 0014-4827<br/>page 213, right-hand column, last paragraph<br/>page 209; figure 1</p> | 14,15,17              |
| X  | <p>US 2003/143539 A1 (BERTUCCI FRANCOIS ET AL) 31 July 2003 (2003-07-31)<br/>paragraph '0080!; claims<br/>2,11-17,19,26,31,43,44,57,58; table 4;<br/>sequences 30,31</p>  | 3,4,12,<br>17,18      |
| X  | <p>SALEH YOUSIF ET AL: "Effects of combined in vivo treatment of transplantable solid mammary carcinoma in wistar rats using vitamin E and cysteine peptidase inhibitors from human placenta."<br/>JOURNAL OF EXPERIMENTAL THERAPEUTICS &amp; ONCOLOGY. 2003 MAR-APR,<br/>vol. 3, no. 2, March 2003 (2003-03), pages<br/>95-102, XP001204013<br/>ISSN: 1359-4117<br/>the whole document</p>           | 14,15,17              |
| X  | <p>SCORILAS ANDREAS ET AL: "Determination of cathepsin B expression may offer additional prognostic information for ovarian cancer patients."<br/>BIOLOGICAL CHEMISTRY. 2002 JUL-AUG,<br/>vol. 383, no. 7-8, July 2002 (2002-07),<br/>pages 1297-1303, XP009040871<br/>ISSN: 1431-6730<br/>the whole document</p>   | 3,4,17                |

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.      |
|------------|--|----------------------------|
| A          | <p>CLAHSEN PIETER C ET AL: "p53 Protein accumulation and response to adjuvant chemotherapy in premenopausal women with node-negative early breast cancer"<br/>JOURNAL OF CLINICAL ONCOLOGY,<br/>vol. 16, no. 2, February 1998 (1998-02),<br/>pages 470-479, XP009040794<br/>ISSN: 0732-183X<br/>abstract</p> <p>-----</p>  | 3-5,12,<br>14,15,<br>17,18 |
| A          | <p>GASPARINI G ET AL: "Expression of bcl-2 protein predicts efficacy of adjuvant treatments in operable node-positive breast cancer."<br/>CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. FEB 1995,<br/>vol. 1, no. 2, February 1995 (1995-02),<br/>pages 189-198, XP001204032<br/>ISSN: 1078-0432<br/>abstract</p> <p>-----</p> | 3-5,12,<br>14,15,<br>17,18 |
| A          | <p>MUSS HYMAN B ET AL: "C-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer"<br/>NEW ENGLAND JOURNAL OF MEDICINE,<br/>vol. 330, no. 18, 1994, pages 1260-1266,<br/>XP009040793<br/>ISSN: 0028-4793<br/>abstract</p> <p>-----</p>  | 3-5,12,<br>14,15,<br>17,18 |
| A          | <p>KOPP R ET AL: "Predictive relevance of soluble CD44v6 serum levels for the responsiveness to second line hormone- or chemotherapy in patients with metastatic breast cancer"<br/>ANTICANCER RESEARCH,<br/>vol. 21, no. 4B, July 2001 (2001-07),<br/>pages 2995-3000, XP001204324<br/>ISSN: 0250-7005<br/>abstract</p> <p>-----</p>  | 3-5,12,<br>14,15,<br>17,18 |
| A          | <p>MUNSTER P N ET AL: "PREDICTIVE FACTOR FOR THE RESPONSE TO ADJUVANT THERAPY WITH EMPHASIS IN BREAST CANCER"<br/>BREAST CANCER RESEARCH, CURRENT SCIENCE,<br/>LONDON, GB,<br/>vol. 3, no. 6, 2001, pages 361-364,<br/>XP008016080<br/>ISSN: 1465-5411<br/>the whole document</p> <p>-----</p>   | 3-5,12,<br>14,15,<br>17,18 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/011009

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| US 2003143539 A1                          | 31-07-2003          | AU 3479902 A               | 18-06-2002          |
|   |                     | CA 2430981 A1              | 13-06-2002          |
|   |                     | EP 1353947 A2              | 22-10-2003          |
|   |                     | WO 0246467 A2              | 13-06-2002          |
| <hr/>                                     |                     |                            |                     |

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## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 11  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
3-5, 12, 14-15, 17-18(partly)

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 11

The subject-matter of claim 11 is directed to a method of treatment. However, the method is defined by the method of determining expression level of (a) marker gene(s) and is not defined by features of the treatment as such. Claim 11, thus, represents a combination of two different and irreconcilable types of process claims. Steps (i) of claim 11 relates to a process of identifying and step (ii) relates to a process of using. Step (ii) builds on the intellectual knowledge gained by steps (i), rather than defining a specific medicament or a specific use. This results in a claim which lacks technical features to an extent that it cannot be searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1 : Claims 3-5,12,14-15,17-18 (partly)

Methods of detecting, diagnosing, screening, monitoring and giving prognosis about a neoplastic disease in a subject; methods of screening a plurality of subjects for a neoplastic disease; and methods of screening for substances with curative effect on a neoplastic disease by determining the expression level of at least one marker gene and comparing the expression with a reference pattern wherein the marker gene consists of SEQ ID NO:1.

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Inventions 2-114: Claims 3-5,12,14-15,17-18 (partly)

Methods of detecting, diagnosing, screening, monitoring and giving prognosis about a neoplastic disease in a subject; methods of screening a plurality of subjects for a neoplastic disease; and methods of screening for substances with curative effect on a neoplastic disease by determining the expression level of at least one marker gene and comparing the expression with a reference pattern, wherein the marker gene consists of one of SEQ ID NO:2-3, 9-10, 14, 16-17, 19-21, 28, 30, 33, 35-39, 41-42, 44-49, 52-54, 56-57, 59-60, 62-64, 66-67, 70-73, 75-80, 84-85, 88-91, 93-97, 99, 102-103, 107, 109-112, 114-123, 125-127, 130-131, 134-137 or 139-165

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Inventions 115-158: Claims 1-10,12-24 (partially)

Methods of characterizing the state of, detecting, diagnosing, screening, monitoring and giving prognosis about a neoplastic disease in a subject; methods of screening a plurality of subjects for a neoplastic disease; and methods of screening for substances with curative effect on a neoplastic disease by determining the expression level of at least one marker gene and comparing the expression with a reference pattern, wherein the marker gene consists of one of the marker genes from Table 2, namely SEQ ID NOs: 4-8, 11-13, 15, 22-27, 29, 31-32, 40, 43, 50, 55, 58, 61, 68-69, 74, 81-83, 98, 100-101, 104-106, 108, 113, 124, 128-129, 132-133 or 138. Further, kits containing 47 primer pairs and probes or only probes and methods for determining the expression of all of the marker genes from Table 2.

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Inventions 159-161: Claims 1-2,6-10,12-13,16-24 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods of characterizing the state of a neoplastic disease in a subject; methods of screening a plurality of subjects for a neoplastic disease; and methods of screening for substances with curative effect on a neoplastic disease by determining the expression level of at least one marker gene and comparing the expression with a reference pattern, wherein the marker gene consists of one of SEQ ID NOs:51, 65 or 92 and a kit containing primers and probes suitable for determining the expression of all 47 marker genes of Table 2.

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Inventions 162-181: Claims 2,4-10,12-13,15,17-18,20,22,24

Methods of detecting, diagnosing, screening, monitoring and giving prognosis about a neoplastic disease in a subject; methods of screening a plurality of subjects for a neoplastic disease; and methods of screening for substances with curative effect on a neoplastic disease by determining the expression level of at least one marker gene and comparing the expression with a reference pattern, wherein the marker gene is one of the marker genes with SEQ ID Nos 472-491. Further, kits containing 20 primer pairs and probes or only probes and methods for determining the expression of all 20 marker genes having SEQ ID Nos 472-491.

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